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New 9,11-Ethano-7-oxo-13-thia Prostanoids

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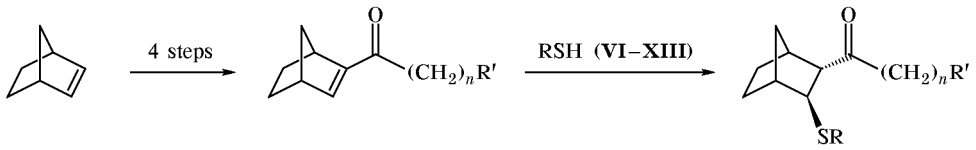
Abstract—New 9,11-ethano analogs of prostaglandin endoperoxides containing a sulfur atom in position *13* were synthesized by nucleophilic addition of thiols at the polarized double bond of 2-acylbicyclo[2.2.1]hept-2-enes. Physicochemical properties and biological activity of the products were studied.

Prostaglandin endoperoxides (PGG_2, PGH_2) are key intermediates in the biosynthesis of primary prostaglandins (PGE_2, PGD_2, PGF_2, etc.), thromboxans (TXA_2, TXB_2), and prostacyclin (PGI_2) from arachidonic acid. TXA_2 and PGI_2 are cellular bioregulators which exhibit opposite physiological effects. TXA_2 is a powerful vasoconstrictor which induces thrombocyte aggregation, whereas PGI_2 posseses a high vasodilating and antiaggregation activity. In the absence of pathologies, the action of TXA_2 is counterpoised by the action of PGI_2. Imbalance of these bioregulators induces serious damage of the cardiovascular and other systems [1, 2]. Native TXA_2 and PGI_2 are local hormones which are formed in cells at a very low concentrations, and they act instantaneously. Therefore, from the viewpoint of practical medicine it is important to have a chance of controlling the TXA_2/PGI_2 ratio with the aid of more stable mimetics or antagonists, as well as of inhibitors of biosynthesis of these bioregulators. In this connection, of particular interest are 9,11-ethano-prostanoids, i.e., carbacyclic analogs of PGH [3].

Studies of the structure–activity relations in the series of PGH carbacyclic analogs have shown [4] that structural variations in the prostanoid ω-chain, including introduction of a heteroatom thereinto, strongly affects the kind of biological activity. We made an attempt to synthesize 9,11-ethano-7-oxo-13-thia prostanoids starting from 2-acylbicyclo[2.2.1]hept-2-enes **II**–**V** which were reported by us previously [5]. The transformation of **II**–**V** into the target 9,11-ethano prostanoids includes the stage of formation of a native or modified ω-chain via conjugate 1,4-addition at the activated double bond.

13-Thia prostanoids were synthesized by nucleophilic addition of thiols at the polarized double bond of acylbicycloheptenes **II**–**V**. The reaction occurs readily, and the sulfur atom adds to the electron-deficient carbon atom at the double bond in a stereoselective fashion, in the *exo* position with respect to the methylene bridge. All the thiols used turned out to be active nucleophiles in the Michael addition to acylbicycloheptenes **II**–**V**. 1,4-Addition of thiols **VI**–**XIII** to enones **II**–**V** smoothly proceeds at room

Scheme 1.



I **II–V** **XIV–XXV**

II, **IV**, **XIV**, **XV**, **XVII**, **XIX**, **XXI**–**XXIV**, *n* = 4; **III**, **XVI**, **XVIII**, **XX**, *n* = 5; **V**, **XXV**, *n* = 6; **VI**, **XIV**, R = C_4H_9; **VII**, **XV**, **XVI**, R = C_6H_{13}; **VIII**, **XVII**, **XVIII**, R = C_8H_{17}; **IX**, **XIX**, **XX**, R = C_6H_5; **X**, **XXI**, R = $C_6H_4NH_2$-4; **XI**, **XXII**, R = CH_2COOH; **XII**, **XXIII**, **XXIV**, R = $CH(CH_3)COOH$; **XIII**, **XXV**, R = $(CH_2)_2CO_2C_2H_5$; **II**, **III**, **XIV**–**XXII**, **XXIV**, R′ = $COOCH_3$; **IV**, **XXIII**, R′ = $COOCH_3$; **V**, **XXV**, R′ = CH_3.

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Table 1. Spectral parameters of compounds **XIV**–**XXV**

Comp. no.	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	IR spectrum, ν, cm^{-1}	$[M]^+$
XIV	0.92 t (3H, CH_3, $^3J_{16,17}$ = 7.0), 1.06 m (1H, *endo*-11′-H), 1.17–1.46 m (5H, 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1H, *anti*-10-H, $^2J_{10,10}$ = 10.0; 2H, CH_2), 1.46–1.70 m (7H: 6H, 3CH_2; 1H, *exo*-11′-H), 1.84 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 10.0), 2.22 br.d (1H, 11-H, $^3J_{11,11'}$ = 4.1), 2.31 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ = 7.0), 2.36–2.51 m [4H, 2H, CH_2C(O), $^3J_{5,6}$ = 6.0; 2H, SCH_2, $^3J_{14,15}$ = 7.2], 2.60 br.d (2H: 1H, *exo*-8-H, $^4J_{8,10}$ = 2.1; 1H, 9-H), 3.12 d.d (1H, *endo*-12-H, $^3J_{8,12}$ = 4.2, $^4J_{10,12}$ = 2.1), 3.66 s (3H, CH_3O)	760, 890, 961, 1015, 1045, 1068, 1110, 1179, 1207, 1265, 1305, 1370, 1445, 1470, 1715 s (C=O), 1748, 2879, 2963	326
XV	0.88 t (3H, CH_3, $^3J_{18,19}$ = 6.4), 1.00–1.15 m (1H, *endo*-11′-H), 1.15–1.47 m [9H: 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1.36 d.m, 1H, *anti*-10-H, $^2J_{10,10}$ = 9.6; 6H, CH_2], 1.47–1.64 m (7H, 3CH_2; 1H, *exo*-11′-H), 1.86 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 9.6), 2.24 br.d (1H, 11-H, $^3J_{11,11'}$ = 4.4), 2.33 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ = 6.9), 2.39–2.57 m [4H; 2.45 t, 2H, CH_2C(O), $^3J_{5,6}$ = 7.0; 2.50 t, 2H, SCH_2, $^3J_{14,15}$ = 7.2], 2.64 br.s (1H, 9-H), 2.69 t.d (1H, *exo*-8-H, 3.18 d.d (1H, *endo*-12-H, $^3J_{8,12}$ = 4.2, $^4J_{10,12}$ = 1.9), 3.67 s (3H, CO_2CH_3)	824, 850, 890, 918, 960, 1009, 1031, 1077, 1108, 1178, 1205, 1257, 1289, 1300, 1370, 1442, 1459, 1710 s (C=O), 1740, 2878, 2955	354
XVI	0.89 t (3H, CH_3, $^3J_{18,19}$ = 6.8), 1.02 m (1H, *endo*-11′-H), 1.21–1.41 m (11H: 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1.35 d.m, 1H, *anti*-10-H, $^2J_{10,10}$ = 9.9; 8H, 4CH_2), 1.56–1.70 m (7H: 1H, *exo*-11′-H; 6H, 3CH_2), 1.84 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 9.8), 2.24 d (1H, 11-H, $^3J_{11,11'}$ = 4.4), 2.31 t (2H, $CH_2CO_2CH_3$, $^3J_{2,3}$ = 7.0), 2.42 t [2H, CH_2C(O), $^3J_{5,6}$ = 6.5], 2.48 d.t (2H, SCH_2, $^3J_{14,15}$ = 7.2, $^2J_{14,14}$ = 1.2), 2.63 br.s (1H, 9-H), 2.66 t.d (1H, *exo*-8-H, $^3J_{8,12}$ = 5.0, $^3J_{8,9}$ = 4.9, $^4J_{8,9'}$ = 1.8), 3.16 d.d (1H, *endo*-12-H, $^3J_{8,12}$ = 5.0, $^4J_{10,12}$ = 1.8), 3.66 s (3H, CH_3O)	740, 850, 880, 927, 975, 1003, 1070, 1081, 1102, 1170, 1200, 1256, 1283, 1294, 1312, 1360, 1432, 1455, 1709 s (C=O), 1740, 2865, 2870, 2926, 2950	368
XVII	0.89 t (3H, CH_3, $^3J_{20,21}$ = 6.6), 1.00–1.09 m (1H, *endo*-11′-H), 1.18–1.43 m (13H: 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1.35 d.m, 1H, *anti*-10-H, $^2J_{10,10}$ = 9.8; 10H, 5CH_2), 1.51–1.65 m (7H: 6H, 3CH_2; 1H, *exo*-11′-H; 1.85 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 9.8), 2.23 br.d (1H, 11-H, $^3J_{11,11'}$ = 4.2), 2.32 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ = 6.9), 2.43 t [2H, CH_2C(O), $^3J_{5,6}$ = 6.2], 2.48 t.d (2H, SCH_2, $^3J_{14,15}$ = 7.8, $^2J_{14,14}$ = 1.3), 2.61 m (1H, 9-H), 2.65 t.d (1H, *exo*-8-H, $^3J_{8,12}$ = 4.6, $^4J_{8,9'}$ = 1.5), 3.17 d.d (1H, *endo*-12-H, $^3J_{8,12}$ = 4.6, $^4J_{10,12}$ = 1.5), 3.66 s (3H, CH_3O)	740, 850, 890, 925, 960, 975, 1006, 1075, 1102, 1170, 1200, 1258, 1296, 1302, 1365, 1433, 1455, 1709 s (C=O), 1740, 2860, 2870, 2926, 2950	382
XVIII	0.89 t (3H, CH_3, $^3J_{20,21}$ = 6.9), 1.04 m (1H, *endo*-11′-H), 1.22–1.41 m (15H: 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1H, *anti*-10-H; 12H, 6CH_2), 1.53–1.69 m (7H, 6H, 3CH_2; 1H, *exo*-11′-H), 1.84 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 9.6), 2.24 br.d (1H, 11-H, $^3J_{11,11'}$ = 4.2), 2.31 t (2H, $CH_2CO_2CH_3$, $^3J_{2,3}$ = 7.4), 2.41 t [2H, CH_2C(O), $^3J_{5,6}$ = 7.4], 2.48 t.d (2H, SCH_2, $^3J_{14,15}$ = 7.8, $^2J_{14,14}$ = 1.3), 2.61 br.s (1H, 9-H), 2.65 t.d (1H, *exo*-8-H, $^3J_{8,12}$ = 4.6, $^4J_{8,9'}$ = 1.5), 3.17 d.d (1H, *endo*-12-H, $^3J_{8,12}$ = 4.6, $^4J_{10,12}$ = 1.5), 3.68 s (3H, CH_3O)	745, 850, 880, 927, 955, 1006, 1105, 1175, 1200, 1258, 1295, 1365, 1435, 1454, 1710 s (C=O), 1740, 2860, 2878, 2930, 2960	396
XIX	1.02–1.19 m (1H, *endo*-11′-H), 1.19–1.48 m (3H: 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1.41 d.m, 1H, *anti*-10-H, $^2J_{10,10}$ = 9.8), 1.48–1.68 m (5H, 4H, 2CH_2; 1H, *exo*-11′-H), 1.94 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 9.8), 2.29 t (2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ = 6.8), 2.33 m [3H, 2H, CH_2C(O), $^3J_{5,6}$ = 6.9; 1H, 11-H], 2.64 br.s (1H, 9-H), 2.76 t.d (1H, *exo*-8-H, $^3J_{8,12}$ = 4.6, $^4J_{8,9'}$ = 1.8), 3.67 s (3H, CO_2CH_3), 3.75 d.d (1H, *endo*-12-H, $^3J_{8,12}$ = 4.6,	906, 917, 944, 992, 1015, 1033, 1060, 1090, 1094, 1165, 1200, 1245, 1278, 1290, 1360, 1406, 1432, 1449, 1477,	346

Table 1. (Contd.)

Comp. no.	^{1}H NMR spectrum, δ, ppm (*J*, Hz)	IR spectrum, ν, cm^{-1}	$[M]^+$
XIX	$^4J_{10,12}$ = 2.0), 7.16 t (1H, 4′-H, C_6H_5), 7.25 d.d (2H, 3′-H, 5′-H, C_6H_5), 7.32 d (2H, 2′-H, 6′-H, C_6H_5)	1584, 1712 s (C=O), 1742, 2861, 2842, 3048, 3067	
XX	1.09 m (1H, *endo*-11′-H), 1.20–1.45 m (5H: 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1.40 d.m, 1H, *anti*-10-H, $^2J_{10,10}$ 10.5; 2H, CH_2), 1.48–1.67 m (5H: 4H, 2CH_2; 1H, *exo*-11′-H), 1.95 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 10.5), 2.23–2.40 m [5H: 2.28 t, 2H, $CH_2CO_2CH_3$, $^3J_{3,4}$ = 7.4; 2H, $CH_2C(O)$; 1H, 11-H], 2.63 br.s (1H, 9-H), 2.76 t.d (1H, *exo*-8-H, $^3J_{8,12}$ = 4.8, $^3J_{8,9}$ = 4.8, $^4J_{8,9'}$ = 1.8), 3.68 s (3H, CO_2CH_3), 3.74 d.d (1H, *endo*-12-H, $^3J_{8,12}$ = 4.8, $^4J_{10,12}$ = 1.8), 7.16 t (1H, 4′-H, C_6H_5), 7.25 d.d (2H, 3′-H, 5′-H, C_6H_5), 7.32 d (2H, 2′-H, 6′-H, C_6H_5)	955, 1029, 1070,1090, 1108, 1175, 1200, 1253, 1260, 1300, 1365, 1410, 1440, 1455, 1480, 1585, 1710, 1740, 2878, 2965, 3062, 3080	360
XXI	1.00–1.14 m (1H, *endo*-11′-H), 1.17–1.43 m (3H: 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1.36 d.m, 1H, *anti*-10-H, $^2J_{10,10}$ = 10.0, $^4J_{10,12}$ = 1.9), 1.43–1.67 m (5H, 4H, 2CH_2; 1H, *exo*-11′-H), 1.94 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 10.0), 2.11–2.42 m [5H, 2H, CH_2COOCH_3; 2H, $CH_2C(O)$; 1H, 11-H], 2.58 br.s (1H, 9-H), 2.70 t.d (1H, *exo*-8-H, $^3J_{8,12}$ = 4.1, $^4J_{8,9'}$ = 1.9), 3.48 d.d (1H, *endo*-12-H, $^3J_{8,12}$ = 4.1, $^4J_{10,12}$ = 2.0), 3.66 s (3H, $COOCH_3$), 6.55 d (2H, 2′-H, 6′-H, C_6H_5), 7.18 d (2H, 3′-H, 5′-H, C_6H_5)	960, 1018, 1110, 1182, 1205, 1220, 1269, 1300, 1372, 1442, 1463, 1506, 1609, 1635 m (δNH), 1715, 1740, 2372, 2880, 2960, 3242, 3382, 3475	361
XXII	0.98–1.13 m (1H, *endo*-11′-H), 1.16–1.49 m (3H: 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1H, *anti*-10-H, $^2J_{10,10}$ = 10.0, $^4J_{10,12}$ = 1.9), 1.62 m (5H: 4H, 2CH_2; 1H, *exo*-11′-H), 1.84 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 10.0), 2.26–2.40 m (3H, 2.34 t, 2H, CH_2COOCH_3, $^3J_{3,4}$ = 7.0; 2.30 d.m, 1H, 11-H), 2.45 t [2H, $CH_2C(O)$, $^3J_{5,6}$ = 6.0], 2.66 br.s (1H, 9-H), 2.76 t.d (1H, *exo*-8-H, $^3J_{8,12}$ = 4.5, $^4J_{8,9'}$ = 1.5), 3.31 m (3H: 1H, *endo*-12-H; 2H, SCH_2), 3.68 s (3H, $COOCH_3$), 10.74 br.s (1H, COOH)	912, 962, 1015, 1050, 1068, 1023, 1155, 1188, 1209, 1270, 1300, 1379, 1415, 1447, 1718 s (C=O), 1739, 2882, 2964, 2382–3550	328
XXIII	1.05 m (1H, *endo*-11′-H), 1.25 m (3H: 1H, *exo*-11′-H; 1H, *exo*-9′-H; 1H, *endo*-9′-H), 1.36 d.m (1H, *anti*-10-H, $^2J_{10,10}$ = 10.0, $^4J_{10,12}$ = 1.6), 1.48 d (3H, CH_3, $^3J_{14,15}$ = 7.2), 1.56 m (4H, 2CH_2), 1.76 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 10.0), 2.28 d (1H, 11-H, $^3J_{11,11'}$ = 4.2), 2.32–2.54 m (4H, 2CH_2), 2.61 br.s (1H, 9-H), 2.76 t.d (1H, 8-H, $^3J_{8,12}$ = 4.3, $^3J_{8,9}$ = 4.3, $^4J_{8,9'}$ = 1.6), 3.37 d.d (1H, *exo*-12-H, $^3J_{8,12}$ = 4.3, $^4J_{10,12}$ = 1.6), 3.41 q (1H, CHS, $^3J_{14,15}$ = 7.2), 10.08 br.s (2H, COOH)	930, 956, 995, 1043, 1065, 1077, 1108, 1159, 1181, 1209, 1239, 1261, 1294, 1317, 1378, 1511, 1554, 1708 s (C=O), 2880, 2400–3460	328
XXIV	1.04 m (1H, *endo*-11′-H), 1.17–1.70 m (13H: 1H, *exo*-11′-H; 1H, *exo*-9′-H; 1H, *endo*-9′-H; 1.36 d.m, 1H, *anti*-10-H, $^2J_{10,10}$ = 10.0, $^4J_{10,12}$ = 1.6; 1.45 d, 3H, CH_3, $^3J_{14,15}$ = 7.2), 1.78 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 10.0), 2.27 d (1H, 11-H, $^3J_{11,11'}$ = 4.2), 2.32–2.48 m (4H, 2CH_2), 2.62 br.s (1H, 9-H), 2.71 t.d (1H, 8-H, $^3J_{8,12}$ = 4.3, $^3J_{8,9}$ = 4.3, $^4J_{8,9'}$ = 1.6), 3.32–3.54 m (2H: 1H, 12-H; 3.44 q, 1H, CHS, $^3J_{14,15}$ = 7.3), 3.68 s (3H, CH_3O), 10.40 br.s (1H, COOH)	959, 1004, 1047, 1064, 1080, 1108, 1176, 1208, 1241, 1260, 1291, 1316, 1371, 1412, 1440, 1452, 1707, 1736, 2878, 2959,2350–3400	342
XXV	0.89 t (3H, CH_3, $^3J_{1,2}$ = 6.6), 1.04 m (1H, *endo*-11′-H), 1.21–1.46 m (14H, 8H, 4CH_2; 3H, OCH_2CH_3; 1H, *exo*-9′-H; 1H, *endo*-9′-H), 1.38 d.m (1H, *anti*-10-H, $^2J_{10,10}$ = 9.9), 1.52–1.66 m (3H: 2H, CH_2; 1H, *exo*-11′-H), 1.84 d.m (1H, *syn*-10-H, $^2J_{10,10}$ = 9.9), 2.26 br.d (1H, 11-H, $^3J_{11,11'}$ = 4.2), 2.41 t [2H, $CH_2C(O)$, $^3J_{5,6}$ = 7.2], 2.57– 2.69 m (4H: 2H, 8-H, 9-H; 2H, C**H**$_2COOC_2H_5$), 2.75 m (2H, CH_2S), 3.21 d.d (1H, 12-H, $^3J_{8,12}$ = 4.3, $^4J_{10,12}$ = 1.9), 4.14 q (2H, CH3C**H**$_2$O, ^3J = 7.2)	935, 954, 1000, 1076, 1115, 1180, 1215, 1242, 1282, 1315, 1345, 1370, 1408, 1455, 1710 s (C=O), 1738, 2865, 2879, 2938, 2962	354

temperature in 1–2 h even in the absence of a catalyst and in such a weakly polar aprotic solvent as benzene. Products **XIV**–**XXV** were formed in high yields (Scheme 1). When the reaction was carried out in the presence of triethylamine or tetramethylguanidine as catalyst, the reaction time shortened to 20 and 10 min, respectively. In all cases, the 1,4-addition products were isolated in 95–98% yield.

Compounds **XIV**–**XXV** were purified by column chromatography or preparative thin-layer chromatography on silica gel. They were isolated as oily substances. Comparison of the spectral data of the reaction mixtures with those of the idividual compounds showed that the addition yields only products with *trans* arrangement of the side chains.

The structure of 13-thia prostanoids is unambiguously confirmed by their spectral data in comparison with those of initial enones. The IR spectra of **XIV**–**XXV** lack absorption bands at 1660 and 1580 cm^{-1}, typical of carbonyl group conjugated with double bond, but a band at 1710–1715 cm^{-1} appears due to saturated ketone moiety. Doublet signal of the olefinic proton (δ 6.85 ppm, Table 1) disappears from the ^1H NMR spectra of the thia analogs, while signals from 8-H (δ 2.65–2.76 ppm, t.d) and 12-H (δ 3.16–3.74 ppm, d.d, J = 4.8, 1.8 Hz) are present together with proton signals from the other structural fragments. Among the latter, a characteristic triplet of the CH_2 group at the sulfur atom at δ 2.48 ppm should be noted (when R is an alkyl group); in the case of compounds **XXIII** and **XXIV**, the corresponding signal is a quartet from the CH proton, which is located at δ 3.41 and 3.44 ppm, respectively. The ^1H NMR signals were assigned on the basis of the data obtained by the double resonance technique.

The *trans* arrangement of the α- and ω-chains was derived from the orientation of 8-H and 12-H. The relative configuration of the latter was established on the basis of the multiplicities of the corresponding signals and the coupling constants $J_{8,12}$ which were compared with those reported in [5]. Unlike *exo*-oriented protons, *endo*-protons in the bicycloheptane ring are involved in a limited number of couplings: They show in the ^1H NMR spectra vicinal couplings with J = 4–6 Hz and, in some cases, long-range *W*-coupling (J = 1–2 Hz) with the *anti*-proton of the methylene bridge. In fact, in the spectra of all compounds **XIV**–**XXV**, the signal assigned to 8-H is a triplet of doublets with a vicinal coupling constant of 4.6–5.0 Hz, located at δ 2.60 to 2.76 ppm. The signal from *endo*-12-H is a doublet of doublets located in a weaker field, δ 3.12–3.76 ppm. A considerable deshielding of 12-H (δ 3.76 ppm) in the spectra of **XIX**, **XX**, and **XXI** is explained by the effect of the benzene ring (phenylthio group).

Signals in the ^{13}C NMR spectra of compounds **XIV**–**XXI** and **XXV** were assigned using the data of [6, 7] for substituted bicycloheptanes, taking into account the known general relations holding in the spectra of norbornane derivatives [8]. The side-chain configuration in prostaglandin endoperoxides and their carbacyclic analogs is established on the basis of the chemical shift of the bridging carbon atom (C^{10}) [6]. *endo*-Substitution in bicyclo[2.2.1]heptane derivatives almost does not affect the position of the C^{10} signal, whereas *exo*-substitution should lead to an upfield shift of 3 ppm per substituent. The chemical shifts of C^{10} in the compounds under study fall into the range from 38.05 to 38.31 ppm (Table 2), which is consistent with δ_C 38 ppm calculated from the data for bicycloheptane. Therefore, the substituents are characterized by *endo,exo*-orientation, i.e., the side chains are arranged *trans*. The chemical shift of C^7 is δ_C 209 ppm, indicating *endo*-orientation of the C^1–C^7 side chain. The signals at δ_C 46 and 63 ppm in the monoresonance spectra are doublets, which suggests that they belong to carbon atoms attached to the *endo*- and *exo*-substituents in the bicycloheptane system. The other signals were assigned on the basis of data for substituted bicycloheptanes [8].

The chemical shifts of carbon atoms of the α-chain containing a carbonyl group in position *7* coincide with those calculated previously by Kwiatkowski and co-workers [7] in two independent ways: from the spectra of methyl heptanoate or 2-heptanone and with the aid of increments for acetyl and methoxycarbonyl groups, respectively. The chemical shift of the carbonyl carbon atom, δ_C 208.7–209.4 ppm, is very consistent with both Kwiatkowski's results and the data for acetone (δ_C 209.6 ppm [8]). Alkyl substitution at the σ-carbon atom induces an additional downfield shift by 2–3 to 13 ppm, depending on the degree of branching.

The signals from the ω-chain were identified on the basis of published data for the corresponding alkanes, acids, and esters. Undoubtedly, the doublet signal at δ_C 32.0 ppm belongs to C^{14} in the α-position with respect to sulfur. Its chemical shift can be compared with those found in [4] for thia analogs of prostaglandin endoperoxides having a sulfur atom in position *14* of the prostanoid chain [9].

Study of biological activity of the compounds prepared showed that some of them exhibit immunostimulating effect.

Table 2. ^{13}C NMR spectra of compounds **XIV**–**XXI** and **XXV**, δ_C, ppm

Atom no.	**XIV**	**XV**	**XVI**	**XVII**	**XVIII**	**XIX**	**XX**	**XXI**	**XXV**
C^1	173.54 s	173.77 s	173.81 s	173.80 s	173.96 s	173.66 s	173.64 s	173.50 s	14.05 q
C^2	33.76 t	33.92 t	33.94 t	33.90 t	33.90 t	33.85 t	33.84 t	33.73 t	22.63 t
C^3	24.96 t	24.62 t	24.69 t	24.57 t	24.77 t	24.50 t	24.65 t	24.37 t	31.72 t, 29.12 t
C^4	–	–	28.80 t	–	28.81 t		28.79 t	–	28.54 t
C^5	23.78 t	23.15 t	23.26 t	23.09 t	23.29 t	23.05 t	23.15 t	23.72 t	23.89 t
C^6	41.59 t	41.75 t	41.89 t	41.69 t	41.91 t	41.76 t	41.82 t	41.61 t	42.16 s
C^7	208.86 s	209.14 s	209.30 s	209.20 s	209.41 s	208.91 s	208.98 s	208.72 s	209.65 s
C^8	63.29 d	63.58 d	63.54 d	63.44 d	63.58 d	62.16 d	62.27 d	61.94 d	63.40 d
C^9	40.57 d	40.72 d	40.70 d	40.68 d	40.71 d	40.98 d	40.97 d	41.06 d	40.74 d
C^{10}	38.10 t	38.21 t	38.19 d	38.16 t	38.21 t	38.31 t	38.36 t	38.05 t	38.21 t
C^{11}	43.54 d	43.77 d	43.75 d	43.67 d	43.77 d	43.37 t	43.43 t	42.86 d	43.74 d
C^{12}	46.20 d	46.53 d	46.49 d	46.36 d	46.53 d	48.28 d	48.41 d	50.44 d	46.30 d
C^{14}	32.08 t	32.58 t	32.60 t	32.52 t	32.56 t	136.29 s	136.27 s	122.67 s	27.33 t
C^{15}	31.68 t	28.58 t	28.56 t	28.51 t	28.58 t	126.18 d	126.13 d	134.78 d	34.98 t
C^{16}	22.01 t	28.70 t	28.69 t	29.05 t	29.04 t	128.82 d	128.80 d	115.28 d	171.95 s
C^{17}	13.64 q	31.47 t	31.46 t	29.21 t	29.21 t	130.24 d	130.21 d	146.13 t	
C^{18}		22.56 t	22.55 t	29.21 t	29.21 t	128.82 d	128.80 d	115.28 d	
C^{19}		13.99 q	13.99 q	31.85 t	31.85 t	126.18 d	126.13 d	134.78 d	
C^{20}		–		22.68 t	22.67 t	–	–		
C^{21}				14.11 q	14.06 q				
CH_2CH_2	28.43 t, 22.98 t	29.74 t, 23.89 t		29.73 t, 23.86 t	29.78 t, 23.89 t	28.37 t, 23.82 t	28.37 t, 23.82 t	28.40 t, 22.87 t	29.31 t, 23.72 t
CH_3O	51.38 q	51.43 q		51.51 q	51.39 q	51.46 q	51.46 q	51.30 q	[a]

[a] C_2H_5O: 14.24 q (CH_3), 60.57 t (OCH_2).

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer (200 MHz) at 25°C using $CDCl_3$ as solvent and TMS as internal reference. The IR spectra were obtained on a UR-20 instrument from samples prepared as thin films. The mass spectra were run on a Varian-MAT-311A mass spectrometer (emission current 1000 mA, energy of ionizing electrons 70 eV, vaporizer temperature 120–150°C, ion source temperature 200°C). The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using ether–hexane (1:1) as eluent. The products were isolated by column chromatography on Kieselgel 600 silica gel with ether–hexane as eluent (gradient elution). The NMR, IR, and mass spectral data are given in Tables 1 and 2.

General procedure for the synthesis of 7-oxo-9,11-ethano-13-thia prostanoids XIV–XXV. Thiol **VI**–**XIII**, 1.1 mmol, was added to a solution of 1 mmol of 2-acylbicyclo[2.2.1]heptene **II**–**V** in 10 ml of dry benzene or chloroform, and the mixture was stirred for 1–2 h at room temperature until the initial enone disappeared. The solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel using hexane–ether as eluent (gradient elution).

Methyl 6-(3-butylthiobicyclo[2.2.1]hept-2-yl)-6-oxohexanoate (XIV) was synthesized from 0.07 g of enone **II** and 0.034 ml of 1-butanethiol (**VI**). Yield 0.092 g 98%. Oily substance.

Methyl 6-(3-hexylthiobicyclo[2.2.1]hept-2-yl)-6-oxohexanoate (XV) was synthesized from 0.11 g of enone **II** and 0.072 ml of 1-hexanethiol (**VII**). Yield 0.161 g (97%). Oily substance.

Methyl 7-(3-hexylthiobicyclo[2.2.1]hept-2-yl)-7-oxoheptanoate (XVI) was synthesized from 0.09 g of enone **III** and 0.06 ml of 1-hexanethiol (**VII**). Yield 0.129 g (97%). Oily substance.

Methyl 6-(3-octylthiobicyclo[2.2.1]hept-2-yl)-6-oxohexanoate (XVI) was synthesized from 0.09 g of

enone **II** and 0.07 ml of 1-octanethiol (**VIII**). Yield 0.143 g (98%). Oily substance.

Methyl 7-(3-octylthiobicyclo[2.2.1]hept-2-yl)-7-oxoheptanoate (XVIII) was synthesized from 0.06 g of enone **III** and 0.05 ml of 1-octanethiol (**VIII**). Yield 0.093 g (98%). Oily substance.

Methyl 6-(3-phenylthiobicyclo[2.2.1]hept-2-yl)-6-oxohexanoate (XIX) was synthesized from 0.08 g of enone **II** and 0.04 ml of benzenethiol (**IX**). Yield 0.114 g (97%). Oily substance.

Methyl 7-(3-phenylthiobicyclo[2.2.1]hept-2-yl)-7-oxoheptanoate (XX) was synthesized from 0.08 g of enone **III** and 0.04 ml of benzenethiol (**IX**). Yield 0.112 g (97%). Oily substance.

Methyl 6-[3-(4-aminophenylthio)bicyclo[2.2.1]-hept-2-yl]-6-oxohexanoate (XXI) was synthesized from 0.05 g of enone **II** and 0.029 g of 4-aminobenzenethiol (**X**). Yield 0.074 g (96%). Oily substance.

Methyl 6-(3-carboxymethylthiobicyclo[2.2.1]-hept-2-yl)-6-oxohexanoate (XXII) was synthesized from 0.07 g of enone **II** and 0.023 ml of mercaptoacetic acid (**XI**). Yield 0.093 g (96%). Crystallizable viscous liquid.

6-[3-(1-Carboxyethylthio)bicyclo[2.2.1]hept-2-yl]-6-oxohexanoic acid (XXIII) was synthesized from 0.075 g of enone **IV** and 0.033 ml of 2-mercaptopropionic acid (**XII**). Yield 0.105 g (95%). Crystallizable viscous liquid.

Methyl 6-[3-(1-carboxyethylthio)bicyclo[2.2.1]-hept-2-yl]-6-oxohexanoate (XXIV) was synthesized from 0.105 g of enone **II** and 0.043 ml of 2-mercaptopropionic acid (**XII**). Yield 0.145 g (95%). Crystallizable viscous liquid.

Ethyl 3-(3-octanoylbicyclo[2.2.1]hept-2-ylthio)-propionate (XXV) was synthesized from 0.08 g of enone **V** and 0.05 ml of 3-mercaptopropionic acid (**XIII**). Yield 0.124 g (96%). Crystallizable viscous liquid.

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